## REMARKS

Claims 1-48 were cancelled, claims 49-52, 54-65, and 68 are rejected under 35 U.S.C. § 112, second paragraph; these claims are further rejected under 35 U.S.C. § 103(a) and are provisionally rejected for nonstatutory obviousness-type double patenting.

**Rejection under 35 U.S.C. § 112, second paragraph**

Independent claim 49, and claims 50-52, 54-65, and 68, which depend therefrom are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for reciting a tradename. This rejection is overcome by the present amendment, which deletes the tradename.

**Rejections under 35 U.S.C. § 103(a)**

The Office rejects claims 49-52, 54-65, and 68, which are directed to methods for inducing new blood vessel growth in myocardial tissue, under 35 U.S.C. § 103(a) as obvious over International Publication No. WO 97/14307 by Isner et al., (hereinafter "Isner") in view of U.S. Patent No. 5,880,090, to Hammond et al. (hereinafter "Hammond"), and U.S. Patent No. 6,605,274 to Dillman et al., (hereinafter "Dillman"). For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

***Isner***

The Examiner states that Isner teaches methods for enhancing angiogenesis by injecting a nucleic acid encoding an angiogenic protein together with an angiogenic factor. The Examiner acknowledges that Isner does not describe the administration of an effective amount of a stem cell factor, a colony stimulating factor, or an effective fragment thereof to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells. The Examiner further acknowledges that Isner does not describe methods for monitoring cardiac function as presently claimed. The Examiner relies on Hammond to provide those elements of the claimed invention that the Examiner states are not present in Isner.

***Hammond***

The Examiner asserts that Hammond describes methods for increasing blood vessel formation in a tissue of a patient. Applicants respectfully disagree. Hammond describes

methods for coating a ***synthetic vascular graft*** with endothelial cells. Such methods are clearly different from the claimed invention which recites methods for inducing blood vessels in myocardial tissue. First, the grafts described by Hammond are entirely synthetic and comprise polyethylene terephthalate and polytetrafluoroethylene. The usefulness of such grafts is limited by their tendency to promote clot formation (column 1, lines 15-26). To overcome such limitations, Hammond describes methods for increasing the number of endothelial cells that ***attach to and coat the surface*** of synthetic grafts (column 1, line 60, to column 2, line 5). Not only are such synthetic grafts plainly distinct from a myocardial tissue, but the process for forming an endothelial coating on such a graft is clearly different from the process required to generate new blood vessel within a tissue. Hammond teaches that endothelialization promoting agents (e.g., GM-CSF, G-CSF) enhance "**adherence of circulating endothelial cells to graft surfaces**, or may stimulate the multiplication of blood-borne endothelial precursors that have become adhered." (column 2, lines 64-67.) Hammond teaches that this process relies on "'fallout endothelialization.' More specifically, it has been proposed that the circulating cells give rise to endothelial coatings of vascular prostheses . . . " Methods for increasing the number of endothelial cells that adhere to and coat a synthetic graft are distinctly different from the multifaceted biological processes that regulate blood vessel formation within a myocardial tissue.

Applicants' specification teaches that the formation of blood vessels in a tissue involves the complex regulation of a variety of endothelial cell functions and activities, including cell migration, proliferation, the formation of endothelial cell sprouts, vascular loop formation, the development of capillary tubes and the subsequent formation of tight junctions and the deposition of new basement membranes (page 2, lines 10-15). Such vascular networks fulfill a critical biological function within the tissue of the subject by providing oxygen and nutrients and removing wastes (page 1, lines 27-30). Hammond's process of coating a synthetic graft with endothelial cells is plainly different from the process of blood vessel formation. Methods for increasing the number of endothelial cells that form an endothelial coating on a vascular prosthesis are distinctly different from Applicants' claimed methods, which provide for the formation of new blood vessels in a myocardial tissue. Hammond clearly fails to teach or suggest such methods.

The endothelialization results obtained by Hammond fail to provide the requisite motivation to combine or the expectation of success to modify the methods of Isner. A thorough reading of Hammond suggests that methods for promoting endothelialization may have undesired side effects that would dissuade the skilled artisan from utilizing the methods described by Hammond. In particular, Applicants invite the Office's attention to Example 1, where Hammond describes grafts having endothelial coatings. Regarding such grafts, Hammond states,

> [T]he BMB grafts implanted for four weeks or longer appeared stiff. Histological studies revealed many **osteocytes with microcalcification in the outer graft wall** of these grafts, but not in the inner wall or intima, even at three months. **In the BMB grafts implanted longer than four weeks, osteoblasts, osteocytes, and microcalcifications were found. These undesirable side effects could affect the long-term utility of such grafts . . .** (column 7, lines 55-63)

Hammond's disclosure of adverse results associated with the endothelialization of grafts teaches away from the use of such methods. In view of this teaching away, one skilled in the art would lack the requisite motivation to introduce changes to the methods of Isner, and would further lack the expectation of success required to introduce such changes.

In sum, Hammond fails to teach or suggest any method for inducing new blood vessel growth in a myocardial tissue of a mammal, much less Applicants' claimed methods, which recite administering an effective amount of a nucleic acid encoding at least one angiogenic protein, and administering an effective amount of at least one angiogenic factor, thereby inducing blood vessel growth in the myocardial tissue and increasing the frequency of endothelial progenitor cells in the mammal. Moreover, one skilled in the art would lack the requisite expectation of success to combine the methods of increasing synthetic graft endothelialization described by Hammond with any other method described in the references cited by the Office.

***Dillmann***

Dillmann describes methods for monitoring the function of a cardiac tissue. The Examiner asserts that it would be obvious for the skilled artisan to modify the method of Isner in view of Hammond and then to monitor the effects of this treatment on cardiac function using the

methods described by Dillmann. Applicants respectfully disagree. Dillmann fails to remedy the deficiencies of the other references cited by the Examiner.

Applicants were the first to discover methods for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal. It is not sufficient that one ***could*** have made the combination, the cited references must suggest the ***desirability*** of making the claimed combination and must further indicate that the combination if made would have succeeded.

Applicants were the first to appreciate that blood vessel growth could be induced using such methods. None of the references cited by the Office, alone or in any combination, teaches or suggests all of the claimed limitations of Applicants' claimed invention. The Office has failed to establish a *prima facie* case of obviousness, and the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

**Double-Patenting Rejection**

Claims 49-52, 54-65, and 68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-61 and 63-66 of co-pending Application No. 10/714,574 in view of Dillmann. With regard to the provisional double patenting rejection over copending application Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

In view of the above amendment and Remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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